Journal of Pioneering Medical Sciences
Received: June 22, 2025 | Accepted: October 25, 2025 | Published: December 05, 2025
Volume 14, Issue 11, Pages 64-73

DOI https://doi.org/10.47310/jpms2025141111

The Dual Role of Autophagy in Health and Disease: Therapeutic Perspectives

Naglaa A. Bayomy[1*], Saad Elshafey[2], Marwa S. Badawi[3], Basem Salama[4], Mohammed M. Ismail[5], Naglaa Mokhtar[6], Abdelnaser Badawy[7], Nawal Salama Gouda[8] and Naglaa M. Shalaby[9]

[1,2,3,5]Department of Anatomy, Faculty of medicine, Northern Border university, Arar, 91431, Saudi Arabia
[1]Histology and Cell Biology Department, Faculty of Medicine, Tanta University, Egypt
[3]Embryology Department, Faculty of Medicine, Sohag University, Sohag, Egypt
[4]Department of Community and family Medicine, Faculty of Medicine, Northern Border University, Arar, 91431, Saudi Arabia
[4]Faculty of Medicine, Al-Azhar University, Egypt
[6,7]Department of Medical Biochemistry, College of Medicine, Northern Border University, Arar, 91431, Saudi Arabia
[6,7]Department of Medical Biochemistry, Faculty of Medicine, Mansoura University, Mansoura City-35516, Egypt
[8,9]Department of Microbiology, Faculty of Medicine, Northern Border University, Arar, 91431, Saudi Arabia
[9]Department of Medical Parasitology, Faculty of Medicine, Mansoura University, Mansoura City-35516, Egypt

Author Designation: [1,6,7,8]Professor, [2]Associate Professor, [3,4,9]Assistant Professor, [5]Lecturer

*Corresponding author: Naglaa A. Bayomy (e-mail: naglaa_@hotmail.com).

©2025 the Author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0

Abstract **Background:** Autophagy is an essential self-degradative process critical for cellular homeostasis, acting as a quality control mechanism by removing damaged organelles, misfolded proteins and intracellular pathogens. While fundamental for cell survival and preventing diseases like cancer and neurodegeneration, its deregulation can paradoxically contribute to pathology. The complex dual role of autophagy, coupled with recent advances in understanding its selective forms, necessitates a consolidated review to bridge the gap between mechanistic insights and therapeutic application. **Methods:** A systematic literature search was conducted using major scientific databases (e.g., PubMed, Scopus, Web of Science) for articles published between January 2015 and March 2025. The search focused on keywords including autophagy, autophagy mechanisms, selective autophagy, mitophagy, autophagy and cancer, autophagy therapeutics and autophagy regulation. Included studies were critically appraised to synthesize data on the core molecular machinery, regulatory pathways and its multifaceted role in disease pathogenesis and prevention. **Results:** The analysis reveals significant progress in delineating the molecular execution of autophagy, particularly the machinery of selective autophagy. We found compelling evidence that specific disruptions in autophagic flux and cargo recognition are foundational to diseases ranging from neurodegenerative disorders to metabolic syndromes and cancer. A key synthesis of the data highlights that autophagy's role is not simply binary (protective vs. destructive) but is highly context-dependent, influenced by cell type, disease stage and genetic landscape. This clarifies its paradoxical functions, acting as a tumour suppressor early in carcinogenesis but promoting tumour survival in established cancers. **Conclusions:** This review consolidates the current understanding that precise modulation of autophagy, rather than its broad inhibition or activation, represents the most promising therapeutic avenue. The findings underscore the critical need to develop agents that target specific forms of selective autophagy. Future research must focus on resolving the spatial and temporal control of autophagic pathways to translate these mechanistic insights into effective clinical interventions for a wide spectrum of human diseases.

Key Words Autophagy, Cellular Clearance, Molecular Regulation, Disease Pathogenesis, Cancer

INTRODUCTION

Cell death occurs through programmed (regulated) or necrotic (uncontrolled) mechanisms. Apoptosis (Type I PCD) is the best-studied programmed pathway, while autophagy (Type II PCD) serves as an alternative. Recent research reveals regulated necrosis (necroptosis), blurring the traditional divide. Other forms like pyroptosis (inflammatory) and ferroptosis (iron-dependent) further diversify cell death mechanisms. These processes are vital for development, immunity and disease, with dysregulation linked to cancer and neurodegeneration [1-2].

Autophagy, derived from the Greek words for "self-eating," is a fundamental cellular recycling process that degrades and recycles damaged organelles and proteins to

maintain cellular homeostasis, particularly during nutrient deprivation or stress. While primarily serving as a pro-survival mechanism that generates energy and building blocks through lysosomal degradation, autophagy also plays crucial roles in preventing various pathologies including cancer, neurodegenerative diseases and infections [3]. Recent studies have demonstrated that beyond its cytoprotective functions, excessive autophagy can lead to a distinct form of programmed cell death called autophagic cell death, which operates independently of apoptotic caspases [4]. Current research continues to elucidate the complex regulatory networks that determine whether autophagy promotes cell survival or triggers cell death, with particular focus on its context-dependent roles in development, immunity and disease pathogenesis [5]. The dual nature of autophagy in cell fate decisions makes it a promising therapeutic target for various pathological conditions.

Despite extensive characterization of the individual molecular components of autophagy and its associated cell death pathway, a critical gap remains in understanding the precise regulatory switches that determine its dualistic role in cellular fate. The fundamental controversy lies in predicting when and why autophagy transitions from a pro-survival mechanism to an executor of cell death, a decision with profound implications for therapeutic intervention in cancer and neurodegenerative diseases. This review is undertaken to synthesize the growing yet fragmented body of evidence on the contextual triggers—such as metabolic status, stress intensity and cell type—that govern this critical switch. By systematically evaluating recent advances in the regulatory networks and crosstalk between autophagic cell death and other cell death pathways.

This review aims to synthesize recent insights into autophagy's dual roles in physiology and pathology, emphasizing molecular regulation and therapeutic relevance. It aims also to resolve existing ambiguities and provide a clearer conceptual framework to guide future research and the development of context-specific therapeutic strategies.

METHODS

This article is based on a narrative literature review, which was chosen due to the breadth and complexity of the topic. To gather relevant literature, an extensive search was conducted across several academic databases, including; PubMed, Scopus and Web of Science were queried for relevant literature published between January 2015 and March 2025. The search utilized a combination of keywords and Boolean operators, including; autophagy, autophagy mechanisms, selective autophagy, mitophagy, autophagy and cancer, autophagy therapeutics and autophagy regulation, mTOR, Beclin-1, LC3, neurodegeneration and metabolic disease. The inclusion criteria were peer-reviewed original research articles and review articles in English that focused on the molecular mechanisms, regulation and disease implications of autophagy. Studies outside the specified date range or those not directly relevant to the core focus of this review were excluded. This process identified over 300 publications, from which the 90 most pertinent and high-quality references were selected for inclusion and critical analysis in this review.

RESULTS

Programed Cell Death Morphologies

Clarke's classification identified three cell death types: Type I (apoptosis) features cell shrinkage and caspase-mediated fragmentation, while Type II (autophagic death) shows autophagosome formation and delayed nuclear changes without DNA fragmentation [4]. Originally viewed as a survival mechanism, autophagy can paradoxically trigger cell death under severe stress through caspase-independent pathways [6]. Modern classifications now include additional regulated death mechanisms like necroptosis and ferroptosis, reflecting our evolving understanding of these processes in development and disease [5]. Current research focuses on the molecular switches determining whether autophagy promotes survival or death, with significant implications for treating cancer and neurodegenerative disorders [7].

While apoptosis (Type I) and autophagy (Type II) are well-known, scientists also observe a mysterious Type III death where cells break down without typical lysosomal involvement. Even more intriguing? Cells often mix these programs-like a biological hybrid engine- showing features of multiple death types at once. This blurring of lines, first noted in 1990 but now better understood, suggests our bodies have backup plans to eliminate damaged cells. Recent research reveals these blended deaths are especially important in cancer and neurodegenerative diseases, forcing us to rethink old classifications [7]. Understanding these nuances could unlock new therapies, proving that even in death, cells follow more than one script."

Mechanisms of Autophagy

Cells maintain their health through three specialized autophagy pathways (Figure 1): *macroautophagy,* where double-membrane *autophagosomes* engulf and deliver cargo to lysosomes; *microautophagy*, where lysosomes directly engulf cytoplasmic material via membrane invagination; and *chaperone-mediated autophagy (CMA),* which uses chaperone proteins (e.g., Hsc-70) to selectively transport proteins across the lysosomal membrane via the LAMP-2A receptor. All three pathways converge at the lysosome for degradation, ensuring efficient recycling of cellular components. This evolutionary conserved process, regulated by Autophagy-related gene *(Atg)* proteins, begins with *phagophore* formation and are crucial for preventing diseases like cancer and neurodegeneration [8-9].

Molecular Regulators

Atg Proteins Initially discovered in yeast, over 30 *Atg* (autophagy-related) genes orchestrate the autophagy process, can be grouped into four functional clusters (1) the *Atg1/ULK1 kinase complex*, triggering autophagy initiation; (2) the *Atg8/LC3 and Atg12* conjugation systems, driving autophagosome membrane expansion; (3) the class III PI3K

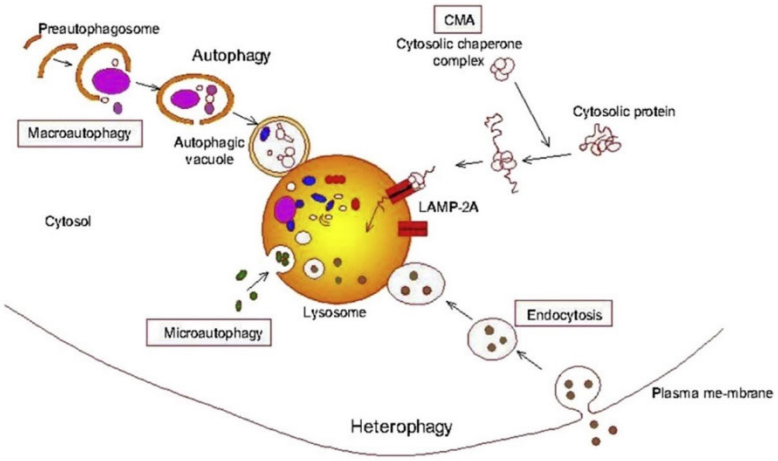

Figure 1: Mammalian cells exhibit three primary autophagy mechanisms: Macroautophagy: A preautophagosome forms and expands to engulf cytosolic material, forming an autophagic vacuole that fuses with a lysosome for degradation, Microautophagy: The lysosome directly engulfs small portions of the cytosol through invaginations of its own membrane and Chaperone-Mediated Autophagy: A selective pathway where a cytosolic chaperone complex delivers specific proteins to the lysosomal receptor LAMP-2A for translocation and degradation [4]. CMA, Chaperone-Mediated Autophagy; LAMP-2A, Lysosome-Associated Membrane Protein type 2A.

complex (including Beclin-1/Atg6), regulating vesicle nucleation; and (4) Atg9 and associated proteins, facilitating membrane supply and recycling. Once formed, autophagosomes fuse with lysosomes, where their cargo is broken down into reusable amino acids and lipids, sustaining cellular metabolism [3,10]. Dysregulation of these Atg-dependent steps is linked to diseases like cancer and neurodegeneration, highlighting their therapeutic potential [11].

Atg1/ULK1 Kinase Complex

In mammalian cells, phagophore membranes primarily emerge from the ER, though they dynamically engage with other compartments like the Golgi, endosomes, and—under specific conditions—the nuclear envelope [12-13]. The ULK1 kinase complex (homologous to yeast Atg1) initiates autophagy by activating Atg9-mediated lipid recruitment to the growing phagophore, a process tightly regulated by mTORC1. mTORC1 suppresses autophagy by phosphorylating ATG13, disrupting its interaction with ULK1 in nutrient-rich conditions [14]. While ULK1 is essential for selective autophagy in reticulocytes [15], the functional redundancy between ULK1 and ULK2 in broader mammalian contexts remains unresolved.

Class III PI3K Complex

The class III PI3K Vps34, in complex with Beclin-1 (Atg6), plays a key role in autophagy by generating phosphatidylinositol-3-phosphate (PI3P) to promote phagophore expansion and recruit ATG proteins (3). Unlike other PI3Ks, Vps34 exclusively uses PI as a substrate, making it critical for autophagosome formation [16]. Beclin-1, frequently mono-allelically deleted in breast, ovarian and prostate cancers, suggests autophagy's tumor- suppressive role [17]. The exact composition of Vps34-Beclin-1 complexes at the ER depends on nutrient-sensing pathways, though their regulation remains incompletely understood [18].

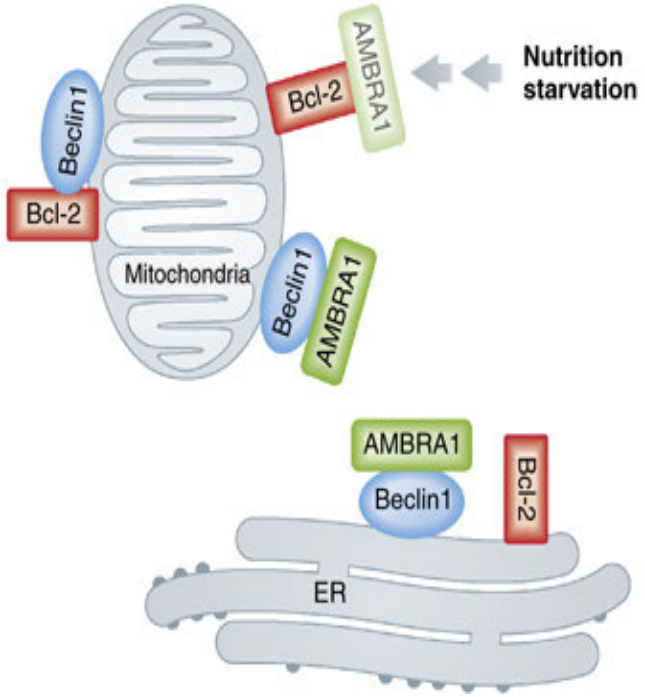

Figure 2: The interaction of Beclin-1 with Bcl-2. Under normal conditions, the autophagy protein Beclin 1 is kept inactive through its binding to Bcl-2 on the mitochondria, while also being tethered by AMBRA1.Upon nutrient starvation, cellular signals cause the release of both AMBRA1 and Beclin 1. The active AMBRA1-Beclin 1 complex then translocates to the endoplasmic reticulum (ER) to trigger the formation of the autophagosome, thereby activating the autophagy pathway [4]. AMBRA1, Activating Molecule in Beclin 1-Regulated Autophagy; Bcl-2, B-cell lymphoma 2 (an anti-apoptotic protein); ER, Endoplasmic Reticulum

The Interaction of Beclin-1 with Bcl-2

The interaction between Beclin-1 and anti-apoptotic proteins Bcl-2/Bcl-XL at the ER membrane inhibits autophagy by preventing Beclin-1 from binding to Vps34 (Figure 2) [19]. This regulatory mechanism involves the BH3 domain of Beclin-1 and is reversed during starvation when JNK1 phosphorylates Bcl-2, releasing Beclin-1 to initiate. Bcl-2 thus exhibits dual functions: (1) its mitochondrial localization prevents apoptosis by blocking cytochrome c release, while (2) its ER-localized pool suppresses autophagy through Beclin-1 sequestration [20]. This regulatory switch determines cell fate decisions between survival and autophagic cell death.

Autophagy progression is governed by ubiquitin-like conjugation systems that orchestrate membrane dynamics. The ATG12-ATG5-ATG16L1 complex, for instance, is essential for initiating phagophore elongation and facilitating the subsequent lipidation of LC3, a key step in autophagosome formation [8,21]. While the molecular details are complex, the functional outcome is a tightly coordinated expansion of the phagophore membrane. It is important to note that unlike the inducible lipidation of LC3, the conjugation of ATG5-ATG12 occurs constitutively, which is why the former is a more reliable marker for monitoring autophagic activity [5].

LC3 Processing

The conversion of the ubiquitin-like protein LC3-I to its lipidated, membrane-bound form, LC3-II, is a central event in autophagy. This processing, mediated by a cascade of Atg enzymes, is indispensable for phagophore expansion and cargo recruitment. The presence of LC3-II on autophagosomal membranes makes it a cornerstone biomarker for assessing autophagic flux, with its levels directly correlating with the number of autophagosomes [22-23].

Capture of Random or Selective Targets for Degradation

Growing evidence shows that phagophore membranes selectively engulf protein aggregates and organelles through LC3B-II, which acts as a docking site for adaptor proteins like p62/SQSTM1. These adaptors bind both ubiquitinated cargo (e.g., damaged mitochondria, protein clumps) and LC3B-II, targeting them for degradation [6]. Mutations in p62/SQSTM1 disrupt this process, leading to diseases like Paget's bone disorder, where impaired protein turnover causes bone deformities [24]. Other adaptors, such as NBR1, play similar roles in clearing ubiquitinated debris, highlighting the system's redundancy [25].

Fusion with the Lysosome

Following phagophore closure, the newly formed autophagosome undergoes sequential fusion with endosomal compartments before ultimately merging with lysosomes to form an autolysosome. Initial interactions with early and late endosomes help acidify the vesicle and deliver essential membrane fusion components [26]. This process depends on Rab7 GTPase activity [27] and involves Presenilin-1, whose dysfunction links impaired autophagy to Alzheimer's pathology [28].

Microtubules facilitate autophagosome-lysosome fusion, as demonstrated by inhibitors like nocodazole that disrupt this transport [29]. Within lysosomes, cathepsins B/D degrade engulfed material [30], while LAMP-1/2 proteins enable membrane stability - their loss causes autophagosome accumulation [31]. Notably, LAMP-2 mutations cause Danon disease, characterized by cardiac autophagic vacuoles and hypertrophy [32].

Atg5/Atg7-Independent Autophagy

While ATG5- and ATG7-dependent autophagy is essential for neonatal survival during starvation [33], recent studies reveal an alternative pathway independent of these canonical genes [34]. This non-canonical autophagy bypasses LC3 processing, instead generating autophagosomes directly from late endosomes and trans-Golgi membranes [35]. The pathway plays specialized roles, particularly in mitochondrial clearance during reticulocyte maturation.

Autophagy functions as a vital cellular quality control mechanism, maintaining homeostasis by continuously degrading damaged organelles and misfolded proteins under basal conditions [10]. This self-digestive process is dramatically upregulated during nutrient deprivation, serving as a critical survival mechanism by recycling cellular components [36]. Multiple stress signals including hypoxia, infection and therapeutic treatments activate autophagy through complex regulatory networks that converge on mTOR-dependent and independent pathways [3,37]. The core

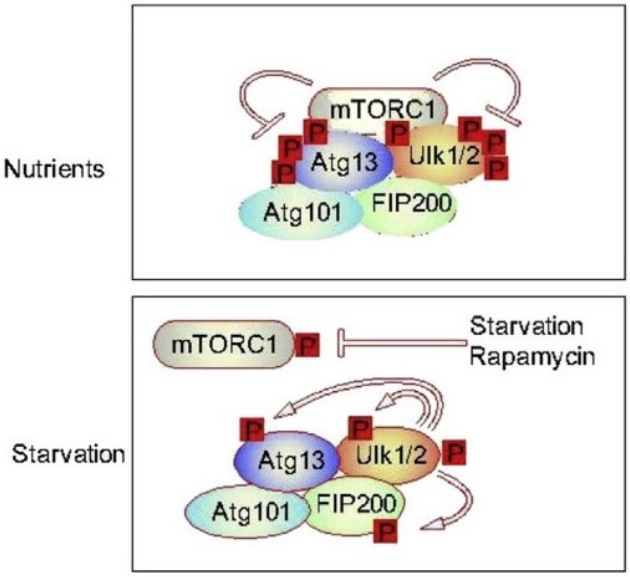

Figure 3: Nutrient-Rich (mTORC1 ON): Active mTORC1 phosphorylates and inhibits the Ulk1/2-Atg13-FIP200-Atg101 complex, blocking autophagy. Starvation/Rapamycin (mTORC1 OFF): mTORC1 inhibition activates the Ulk1/2 complex, triggering autophagosome formation [4]. mTORC1, Mechanistic Target of Rapamycin Complex 1; Ulk1/2, Unc-51 like autophagy activating kinase ½; Atg, Autophagy-related gene protein; FIP200, FAK-family Interacting Protein of 200 kDa.

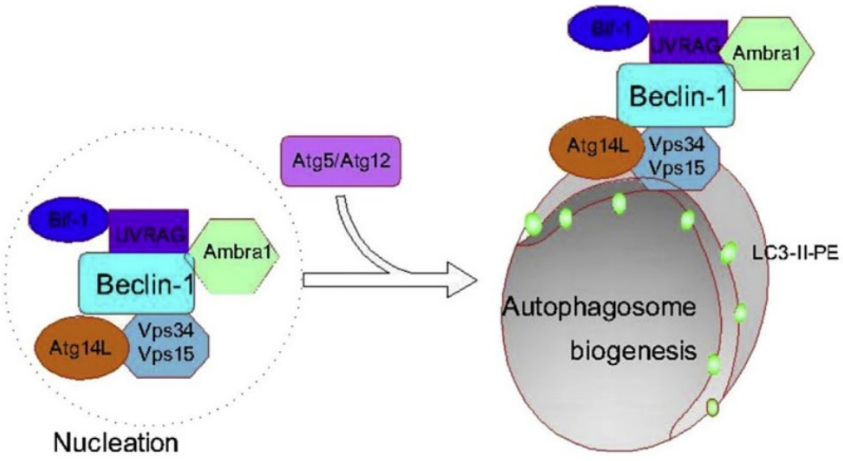

Figure 4: Autophagy Pathway: PI3K complex. The core autophagy initiation complex containing Vps34, Vps15 and Beclin-1. Atg14L-binding complex drives autophagosome nucleation UVRAG/Ambra1 regulate complex activity. The complex produces phosphatidylinositol 3-phosphate to form the phagophore, which is conjugated to LC3 (forming LC3-II-PE) to create the mature autophagosome [4]. PI3K, Phosphoinositide 3-kinase; Vps, Vacuolar protein sorting; Atg, Autophagy-related gene protein; UVRAG, UV radiation resistance-associated gene; LC3-II-PE, Microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine.

autophagy machinery involves key regulators such as ULK1 (the mammalian Atg1 homolog) for organelle clearance and Beclin-1 for alternative autophagy pathways, demonstrating the system's remarkable plasticity in responding to diverse cellular demands (Figure 3) [38].

mTOR and AMPK Pathway in Autophagy Regulation

The mechanistic target of rapamycin (mTOR) serves as a critical signaling hub that coordinates cellular growth with autophagic activity [39]. This conserved kinase integrates inputs from nutrient-sensing pathways (AMPK), growth factors (PI3K-Akt) and oxygen availability to either promote anabolism or activate catabolic autophagy [40]. A network of signaling pathways converges to regulate autophagy, with mTOR acting as a master sensor. In essence, growth-promoting signals (e.g., via PI3K-Akt) activate mTOR to suppress autophagy, while catabolic stresses (e.g., energy depletion via AMPK, hypoxia via HIF-1α) inhibit mTOR to induce it [41-44]. This regulatory nexus allows the cell to precisely adjust its degradative capacity in response to the metabolic environment.

During starvation, inhibited mTOR activity triggers autophagy initiation through the ULK1-ATG13-FIP200 complex, where dephosphorylated ATG13 promotes ULK1 kinase activity [45]. This process is further amplified by AMPK-mediated phosphorylation of ULK1, while S6K1 phosphorylation suppresses autophagosome formation [46].

Hypoxia induces autophagy through both HIF-1α-dependent transcription [47] and HIF-independent mechanisms involving AMPK/REDD1-mediated mTOR inhibition [48]. These adaptive responses enable cells to degrade excess organelles like ER and mitochondria when oxygen is limited, preventing oxidative damage [49]. The coordinated regulation by nutrient and oxygen sensors highlights autophagy's role as a stress adaptation mechanism [50].

The class I PI3K-Akt signaling pathway serves as a critical regulator of cellular growth by suppressing autophagy through mTOR activation (Fig. 4) [51]. Conversely, the tumor suppressor PTEN counteracts this pathway to promote autophagy, with PTEN mutations frequently observed in cancers exhibiting impaired autophagic flux [52]. The autophagy- specific PI3K complex (containing Beclin-1, ATG14 and VPS34) initiates phagophore formation, a process inhibited by 3-methyladenine (3-MA) through VPS34 blockade [53]. Notably, the death-associated protein kinase (DAPK) family induces both autophagy and programmed cell death, suggesting therapeutic potential in oncology [54]. These opposing signaling cascades demonstrate how autophagy sits at the crossroads of cellular metabolism and cancer biology.

Autophagy is tightly controlled by a balance of opposing molecular forces. On one hand, growth-promoting pathways like PI3K-Akt activate mTOR to put the brakes on autophagy, a mechanism often exploited by cancer cells. On the other hand, tumor suppressors like PTEN and specialized complexes involving Beclin-1 work to initiate autophagy and counteract this suppression. This delicate balance positions autophagy at the very heart of cellular decision-making, where its activation or inhibition can tip the scales between cell survival and death, making it a compelling target for cancer therapy

The Relationship between Autophagy and Apoptosis

Emerging research reveals an intricate crosstalk between autophagy and apoptosis, where these pathways can cooperate, compensate or antagonize each other depending on cellular context [4]. While molecularly distinct, they often co-occur in response to stress, with autophagy either promoting cell survival (e.g., protecting cancer cells from DNA damage) or facilitating death (e.g., in imatinib-treated

Kaposi sarcoma) [55]. The relationship is bidirectional - autophagy inhibition can sensitize tumors to radiotherapy, while in HIV-infected T-cells, autophagy becomes essential for subsequent apoptotic death [56].

Three key functional relationships exist:

- **Cooperative death**: Simultaneous activation in prostate cancer with proteasome inhibitors [57]
- **Protective autophagy**: Maintains genomic stability in tumor cells [58]
- **Prerequisite autophagy**: Required for apoptosis in viral infections [59]

Physiology and Pathology or Autophagy in Health and Disease

Fundamental Roles in Cellular and Organismal Physiology: Autophagy serves as a critical survival mechanism during stress (starvation, hypoxia, infection), enabling cells to recycle nutrients and maintain homeostasis by degrading proteins, lipids and organelles [10]. This evolutionarily conserved process is vital during metabolic transitions, such as neonatal adaptation, where it sustains energy production after placental nutrient loss [33]. Impairing autophagy triggers rapid cell death under nutrient deprivation, highlighting its essential protective role [60].

Beyond stress responses, autophagy drives developmental processes like embryogenesis. It eliminates maternal cytoplasmic components (e.g., mRNAs) and paternal mitochondria post-fertilization, ensuring healthy embryonic maturation [61]. These dual roles underscore autophagy's fundamental importance in both survival and life-cycle transitions.

Autophagy facilitates tissue remodeling during embryogenesis by clearing apoptotic debris and drives differentiation of erythrocytes, neurons and immune cells through cytoplasmic reorganization [62]. It maintains immune cell homeostasis and self-tolerance by regulating lymphocyte survival and antigen presentation [63]. Caloric restriction-induced autophagy extends lifespan across species by removing damaged organelles and protein aggregates, linking its quality-control function to anti-aging mechanisms [64].

Quality Control in Health, Aging and Major Organ Systems

As a critical cellular quality-control mechanism, autophagy removes toxic protein aggregates (e.g., amyloid-β in Alzheimer's, α-synuclein in Parkinson's), damaged mitochondria and pathogens [10]. Its dysregulation drives neurodegeneration, liver fibrosis and cardiac pathologies—autophagy impairment exacerbates protein aggregation in neurons, while excessive activation promotes fibrotic tissue remodeling [65-66]. In cardiovascular systems, basal autophagy sustains cardiomyocyte homeostasis, whereas stress-inducible autophagy modulates outcomes in hypertension and ischemia-reperfusion injury [67].

In the pancreas, Autophagy sustains pancreatic β-cell function by maintaining organelle quality and insulin secretion [68]. In the liver, autophagy (lipophagy) breaks down lipid droplets to prevent hepatic steatosis. Impaired hepatic autophagy drives metabolic dysfunction, exacerbating insulin resistance and NAFLD progression [66].

Immunity and Infection

In immunity, autophagy clears intracellular pathogens (e.g., *Salmonella*, SARS-CoV-2) and regulates inflammatory responses. Genetic variations in autophagy-related genes like ATG16L1 and IRGM are linked to increased susceptibility to inflammatory diseases such as Crohn's disease, highlighting its role in maintaining immune homeostasis [69].

A Double-Edged Sword in Metabolic Regulation

The role of autophagy in metabolism is complex and tissue-specific. Decreases in hepatic autophagy are observed in models of obesity and insulin resistance and restoring it alleviates these defects [70-71]. Conversely, autophagy inhibition in white adipose tissue reduces adiposity and enhances insulin sensitivity by promoting fatty acid oxidation [72]. This tissue-specific duality complicates systemic autophagy modulation, underscoring the need for organ-targeted therapies to address metabolic disorders. Autophagy is also implicated in regulating food intake via the brain, though its role in this process requires further clarification [73].

The Dual Role in Cancer Biology and Therapy

Autophagy exhibits a context-dependent duality in cancer biology, functioning as a tumor-suppressive mechanism in early stages by clearing damaged organelles to limit oxidative DNA damage [6], while later supporting tumor survival under metabolic stress via nutrient recycling [74]. In apoptosis-deficient cancers, autophagy sustains viability during hypoxia or nutrient deprivation, enabling adaptation to harsh microenvironments [75]. Paradoxically, impaired autophagy promotes genomic instability, accelerating tumorigenesis, while its hyperactivation aids advanced tumors in evading therapy [76]. Therapeutic strategies now aim to induce autophagy for cancer prevention in high-risk contexts and inhibit it in advanced tumors to enhance treatment efficacy [77].

Blocking autophagy, a process that helps cancer cells survive under stress can enhance treatment effectiveness by pushing these cells toward death. Interestingly, many standard cancer therapies (like chemotherapy and targeted drugs) inadvertently activate autophagy, which may weaken their impact. To counter this, researchers are testing combinations of traditional treatments with hydroxychloroquine, an antimalarial drug that blocks autophagy by preventing lysosomes from breaking down cellular waste. Early-phase clinical trials (e.g., NCT04132505 for pancreatic cancer) have explored this

approach, though newer, more precise autophagy inhibitors are now in development to improve outcomes [55,78].

Autophagy plays a dual role in cancer, acting as both a protector and promoter depending on the tumor's stage of growth. In early stages, autophagy helps prevent cancer by removing damaged components from cells, blocking this process might allow abnormal cells to multiply unchecked [79]. However, once tumors grow larger and face nutrient shortages or low oxygen levels (common in poorly vascularized regions), cancer cells rely on autophagy to survive these harsh conditions [80]. Autophagy also shields some tumors from radiation therapy by clearing radiation-damaged mitochondria and delaying cell death, enabling cancer cells to persist [81]. These opposing roles make autophagy a complex but promising target for tailored cancer therapies.

Emerging research highlights how certain cancer therapies leverage autophagy to combat tumors. For example, tamoxifen, a widely used breast cancer treatment, has been shown to activate autophagy by boosting levels of Beclin-1, a key regulator of this process [82]. Meanwhile, mTOR inhibitors like rapamycin, while primarily designed to block cancer cell proliferation by disrupting cell cycle signals, also indirectly stimulate autophagy [83]. This dual action complicates their mechanism but underscores autophagy's nuanced role in treatment efficacy.

Understanding autophagy's shifting roles—from guardian to enabler—is as crucial as studying apoptosis in cancer biology. Continued research into this dynamic process could unlock new strategies to disrupt tumors' survival tactics while protecting healthy cells, offering hope for more effective therapies.

Survival Versus Death Aspects of Autophagy

The scientific community has long debated whether autophagy actively contributes to cell death or serves a protective role. Early skepticism arose from autophagy's well-known function as a recycling mechanism. Under normal conditions, autophagy breaks down and recycles long-lived proteins, organelles like mitochondria and proteins tagged for disposal (ubiquitinated proteins), maintaining cellular health [84]. During stress, such as nutrient deprivation, autophagy is upregulated to help cells adapt and survive [10]. Experiments disrupting autophagy genes in nutrient-starved environments revealed a surge in apoptotic cell death, contradicting the idea of autophagy as a death promoter. Instead, these findings highlighted its role as a survival strategy, ensuring cells endure harsh conditions [85].

The idea that autophagy can drive opposing outcomes raises a key question: How does the same mechanism lead to such different results? While survival-promoting autophagy and autophagy-related cell death share similar structures and core machinery (like vesicles that engulf cellular components), studies reveal critical molecular distinctions. For instance, in L929 mouse cells, artificially induced autophagy with the drug zVAD triggers cell death by selectively breaking down the antioxidant enzyme catalase, a process absents in autophagy activated by nutrient starvation [86]. Similarly, both ceramide (a lipid signaling molecule) and nutrient deprivation activate autophagy through related pathways involving sphingolipids and mTOR inhibition. However, only ceramide-induced autophagy suppresses survival signals (like the Akt pathway) and activates pro-death proteins such as Beclin-1 and BNIP3 [87]. The balance between two sphingolipids, SK1 and S1P, may act as a "switch": high S1P levels favor survival, while low levels tip the scales toward death—a concept termed the "S1P rheostat" [88].

In line with these observations, Levine and coworkers proposed a model of cell survival versus death, regulated by the balance between Beclin-1 and Bcl-2 proteins [89]. Levine's team introduced a compelling "molecular tug-of-war" model to explain how autophagy shifts from promoting survival to driving cell death. Central to this model are two proteins: Beclin-1 (a key autophagy activator) and Bcl-2 (a well-known anti-apoptotic protein). Under normal conditions, high levels of Bcl-2 act as a brake by binding to Beclin-1, keeping autophagy in check. Small increases in Beclin-1-such as during mild stress-tip this balance, triggering controlled autophagy to recycle resources and sustain survival. However, if Beclin-1 surges beyond what Bcl-2 can neutralize, autophagy spirals out of control, leading to cell death. This idea gained support when mutant versions of Beclin-1, engineered to *avoid* binding Bcl-2, caused rampant autophagy and killed cells—a clear sign that the Beclin-1/Bcl-2 interaction acts as a life-or-death switch [90].

The context-dependent nature of autophagy is starkly revealed when comparing its role across major disease classes. In neurodegenerative diseases like Alzheimer's and Parkinson's, the fundamental problem is typically a *loss of autophagic function*, leading to the accumulation of toxic protein aggregates; the therapeutic goal is therefore to *restore* autophagy [10,63]. Conversely, in advanced cancer, autophagy is often *hijacked and hyperactivated* to fuel tumor survival, creating a rationale for its *inhibition* [6, 80]. The most complex and controversial landscape may be in metabolic diseases like NAFLD and diabetes, where autophagy's role is highly tissue-specific—protective in the liver [66, 70] but potentially detrimental in adipose tissue [72]. This duality presents a significant therapeutic challenge: how can we systemically modulate a process that has opposing functions in different organs? A central, unresolved question cutting across all these fields is identifying the precise molecular switches that determine whether autophagy promotes survival or death and how to therapeutically manipulate this switch without causing catastrophic side effects.

This review integrates recent mechanistic data with clinical perspectives, providing a comprehensive synthesis of autophagy's dual role. However, the review is limited by the lack of quantitative analysis and absence of systematic selection criteria.

CONCLUSIONS

All data presented above underline the importance of the cellular context created by the combinatory activation/ inactivation of pro-survival or death pathways, intracellular levels of key regulatory molecules and the regulation of selective degradation in converting autophagy from a protective mechanism to a killing machine. These advancements promise to refine our understanding of autophagy's role in cellular survival/death decisions and its implications across pathologies.

Limitations

The review is limited by its narrative design and lack of quantitative synthesis. Future studies should integrate systematic meta-analyses, explore tissue-specific autophagy regulation and assess therapeutic interventions in clinical settings.

REFERENCES

[1] Green, Douglas R. "The coming decade of cell death research: Five riddles." *Cell*, vol. 177, no. 5, 2019, pp. 1094–1107. https://doi.org/10.1016/j.cell.2019.04.024.

[2] Tang, Daolin *et al.* "The molecular machinery of regulated cell death." *Cell Research*, vol. 29, no. 5, 2019, pp. 347–364. https://doi.org/10.1038/s41422-019-0164-5.

[3] Dikic, Ivan and Zvulun Elazar. "Mechanism and medical implications of mammalian autophagy." *Nature Reviews Molecular Cell Biology*, vol. 19, no. 6, 2018, pp. 349–364. https://doi.org/10.1038/s41580-018-0003-4.

[4] Sever, Onur N. and Ozgur G. Demir. "Autophagy: Cell death or survive mechanism." *Journal of Oncological Sciences*, vol. 3, 2017, pp. 37–44. https://doi.org/10.1016/j.jons.2017.07.001.

[5] Klionsky, Daniel J. *et al.* "Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)." *Autophagy*, vol. 17, no. 1, 2021, pp. 1–382. https://doi.org/10.1080/15548627.2020.1797280.

[6] Levy, Jay M.M. *et al.* "Targeting autophagy in cancer." *Nature Reviews Cancer*, vol. 17, no. 9, 2017, pp. 528–542. https://doi.org/10.1038/nrc.2017.53.

[7] Park, Woo, *et al.* "Author correction: Diversity and complexity of cell death: A historical review." *Experimental and Molecular Medicine*, vol. 55, no. 9, 2023, p. 2083. https://doi.org/10.1038/s12276-023-01107-9.

[8] Gubas, Andrei and Ivan Dikic. "A guide to the regulation of selective autophagy receptors." *FEBS Journal*, vol. 289, no. 1, 2022, pp. 75–89. https://doi.org/10.1111/febs.15824.

[9] Aman, Yasaman *et al.* "Autophagy in healthy aging and disease." *Nature Aging*, vol. 1, no. 8, 2021, pp. 634–650. https://doi.org/10.1038/s43587-021-00098-4.

[10] Levine, Beth and Guido Kroemer. "Biological functions of autophagy genes: A disease perspective." *Cell*, vol. 176, nos. 1–2, 2019, pp. 11–42. https://doi.org/10.1016/j.cell.2018.09.048.

[11] Fu, Y. *et al.* "Activating autophagy to eliminate toxic protein aggregates with small molecules in neurodegenerative diseases." *Pharmacological Reviews*, 2025. https://doi.org/10.1016/j.pharmr.2025.100053.

[12] Vargas Duarte, Paola and Fulvio Reggiori. "The organization and function of the phagophore-ER membrane contact sites." *Contact*, vol. 6, 2023, p. 25152564231183898. https://doi.org/10.1177/25152564231183898.

[13] Burd, Christopher G. "Physiology and pathology of endosome-to-Golgi retrograde sorting." *Traffic*, vol. 12, no. 8, 2011, pp. 948–955. https://doi.org/10.1111/j.1600-0854.2011.01188.x.

[14] Hosokawa, Noboru *et al.* "Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy." *Molecular Biology of the Cell*, vol. 20, no. 7, 2009, pp. 1981–1991. https://doi.org/10.1091/mbc.e08-12-1248.

[15] Kundu, Minakshi *et al.* "Ulk1 plays a critical role in the autophagic clearance of mitochondria and ribosomes during reticulocyte maturation." *Blood*, vol. 112, no. 4, 2008, pp. 1493–1502. https://doi.org/10.1182/blood-2008-02-137398.

[16] Nascimbeni, A.C. *et al.* "Phosphatidylinositol-3-phosphate in the regulation of autophagy membrane dynamics." *FEBS Journal*, vol. 284, no. 9, 2017, pp. 1267–1278. https://doi.org/10.1111/febs.13987.

[17] Levine, Beth *et al.* "Development of autophagy inducers in clinical medicine." *Journal of Clinical Investigation*, vol. 125, no. 1, 2015, pp. 14–24. https://doi.org/10.1172/JCI73938.

[18] Tan, Vivian P. and Shigeki Miyamoto. "Nutrient-sensing mTORC1: Integration of metabolic and autophagic signals." *Journal of Molecular and Cellular Cardiology*, vol. 95, 2016, pp. 31–41. https://doi.org/10.1016/j.yjmcc.2016.01.005.

[19] Tran, Sean *et al.* "BECLIN1: Protein structure, function and regulation." *Cells*, vol. 10, no. 6, 2021, p. 1522. https://doi.org/10.3390/cells10061522.

[20] Means, Robert E. and Sophia G. Katz. "Balancing life and death: BCL-2 family members at diverse ER–mitochondrial contact sites." *FEBS Journal*, vol. 289, no. 22, 2022, pp. 7075–7112. https://doi.org/10.1111/febs.16241.

[21] Iriondo, Maria N. *et al.* "Effect of ATG12-ATG5-ATG16L1 autophagy E3-like complex on the ability of LC3/GABARAP proteins to induce vesicle tethering and fusion." *Cellular and Molecular Life Sciences*, vol. 80, no. 2, 2023, p. 56. https://doi.org/10.1007/s00018-023-04704-z.

[22] Galluzzi, Lorenzo *et al.* "Pharmacological modulation of autophagy: Therapeutic potential and persisting obstacles." *Nature Reviews Drug Discovery*, vol. 16, no. 7, 2017, pp. 487–511. https://doi.org/10.1038/nrd.2017.22.

[23] Runwal, G. *et al.* "LC3-positive structures are prominent in autophagy-deficient cells." *Scientific Reports*, vol. 9, no. 1, 2019, p. 10147. https://doi.org/10.1038/s41598-019-46657-z.

[24] Ralston, Stuart H. *et al.* "Diagnosis and management of Paget's disease of bone in adults: A clinical guideline." *Journal of Bone and Mineral Research*, vol. 34, no. 4, 2019, pp. 579–604. https://doi.org/10.1002/jbmr.3657.

[25] Chen, Ruey-Hwa *et al.* "Ubiquitin-mediated regulation of autophagy." *Journal of Biomedical Science*, vol. 26, no. 1, 2019, p. 80. https://doi.org/10.1186/s12929-019-0569-y.

[26] Eskelinen, Eeva-Liisa *et al.* "Seeing is believing: The impact of electron microscopy on autophagy research." *Autophagy*, vol. 7, no. 9, 2011, pp. 935–956. https://doi.org/10.4161/auto.7.9.15760.

[27] Ballabio, Andrea and Juan S. Bonifacino. "Lysosomes as dynamic regulators of cell and organismal homeostasis." *Nature Reviews Molecular Cell Biology*, vol. 21, no. 2, 2020, pp. 101–118. https://doi.org/10.1038/s41580-019-0185-4.

[28] Udayar, Vimal *et al.* "Lysosomal dysfunction in neurodegeneration: Emerging concepts and methods." *Trends in Neurosciences*, vol. 45, no. 3, 2022, pp. 184–199. https://doi.org/10.1016/j.tins.2021.12.004.

[29] Lawrence, Rebecca E. and Roberto Zoncu. "The lysosome as a cellular centre for signalling, metabolism and quality control." *Nature Cell Biology*, vol. 21, no. 2, 2019, pp. 133–142. https://doi.org/10.1038/s41556-018-0244-7.

[30] Nnah, Innocent C. *et al.* "TFEB-driven endocytosis coordinates MTORC1 signaling and autophagy." *Autophagy*, vol. 15, no. 1, 2019, pp. 151–164. https://doi.org/10.1080/15548627.2018.1511504.

[31] Saftig, P. and Rosa Puertollano. "How lysosomes sense, integrate and cope with stress." *Trends in Biochemical Sciences*, February 2021, vol. 46, no. 2, pp. 97–112. https://doi.org/10.1016/j.tibs.2020.09.004.

[32] Endo, Y. *et al.* "Danon disease: a phenotypic expression of LAMP-2 deficiency." *Acta Neuropathologica*, 2015, vol. 129, no. 3, pp. 391–398. https://doi.org/10.1007/s00401-015-1385-4.

[33] Wang, L. *et al.* "The physiological roles of autophagy in the mammalian life cycle." *Biological Reviews of the Cambridge Philosophical Society*, April 2019, vol. 94, no. 2, pp. 503–516. https://doi.org/10.1111/brv.12464.

[34] Galluzzi, Lorenzo *et al.* "Corrigendum: Discovery of Atg5/Atg7-independent alternative macroautophagy." *Nature*, 2016, vol. 533, no. 7601, p. 130. https://doi.org/10.1038/nature16538.

[35] Wang, Y. *et al.* "Role of canonical and noncanonical autophagy pathways in shaping the life journey of B cells." *Frontiers in Immunology*, July 2024, vol. 15, article 1426204. https://doi.org/10.3389/fimmu.2024.1426204.

[36] Palmer, J.E. *et al.* "Autophagy, aging and age-related neurodegeneration." *Neuron*, 2025, vol. 113, no. 1, pp. 29–48. https://doi.org/10.1016/j.neuron.2024.09.015.

[37] Kim, Young Chul and Kun-Liang Guan. "mTOR: a pharmacologic target for autophagy regulation." *Journal of Clinical Investigation*, January 2015, vol. 125, no. 1, pp. 25–32. https://doi.org/10.1172/JCI73939.

[38] Galluzzi, Lorenzo *et al.* "Molecular definitions of autophagy and related processes." *EMBO Journal*, 2017, vol. 36, no. 13, pp. 1811–1836. https://doi.org/10.15252/embj.201796697.

[39] Gargalionis, A.N. *et al.* "mTOR signaling: recent progress." *International Journal of Molecular Sciences*, 2024, vol. 25, no. 5, article 2587. https://doi.org/10.3390/ijms25052587.

[40] Kim, Jae and Kun-Liang Guan. "mTOR as a central hub of nutrient signalling and cell growth." *Nature Cell Biology*, 2019, vol. 21, pp. 63–71. https://doi.org/10.1038/s41556-018-0205-1.

[41] Saxton, Robert A. and David M. Sabatini. "mTOR signaling in growth, metabolism and disease." *Cell*, March 2017, vol. 168, no. 6, pp. 960–976. https://doi.org/10.1016/j.cell.2017. 02.004.

[42] Herzig, Sebastian and Reuben J. Shaw. "AMPK: guardian of metabolism and mitochondrial homeostasis." *Nature Reviews Molecular Cell Biology*, 2018, vol. 19, no. 2, pp. 121–135. https://doi.org/10.1038/nrm.2017.95.

[43] Fu, Weiwei and Guanghui Wu. "Targeting mTOR for anti-aging and anti-cancer therapy." *Molecules*, 2023, vol. 28, no. 7, article 3157. https://doi.org/10.3390/molecules28073157.

[44] Kausar, M.A. *et al.* "Autophagy and cancer: insights into molecular mechanisms and therapeutic approaches for chronic myeloid leukemia." *Biomolecules*, 2025, vol. 15, no. 2, article 215. https://doi.org/10.3390/biom15020215.

[45] Hama, Y. *et al.* "The triad interaction of ULK1, ATG13 and FIP200 is required for ULK complex formation and autophagy." *eLife*, 2024, vol. 13, article RP101531. https://doi.org/10.7554/eLife.101531.1.

[46] Kazyken, Dana *et al.* "Unexpected roles for AMPK in the suppression of autophagy and the reactivation of MTORC1 signaling during prolonged amino acid deprivation." *Autophagy*, September 2024, vol. 20, no. 9, pp. 2017–2040. https://doi.org/10.1080/15548627.2024.2355074.

[47] Wang, Ping *et al.* "Hypoxia inducible factor-1α regulates autophagy via the p27-E2F1 signaling pathway." *Molecular Medicine Reports*, August 2017, vol. 16, no. 2, pp. 2107–2112. https://doi.org/10.3892/mmr.2017.6794.

[48] Chun, Youngran and Jae Kim. "AMPK-mTOR signaling and cellular adaptations in hypoxia." *International Journal of Molecular Sciences*, September 2021, vol. 22, no. 18, article 9765. https://doi.org/10.3390/ijms22189765.

[49] Yang, Min *et al.* "Mitochondrial quality control: a pathophysiological mechanism and therapeutic target for stroke." *Frontiers in Molecular Neuroscience*, January 2022, vol. 14, article 786099. https://doi.org/10.3389/fnmol.2021.786099.

[50] Tian, Xin *et al.* "Targeting the integrated stress response in cancer therapy." *Frontiers in Pharmacology*, 2021, vol. 12, article 747837. https://doi.org/10.3389/fphar.2021.747837.

[51] Guarente, V. and P. Sportoletti. "Lessons, challenges and future therapeutic opportunities for PI3K inhibition in CLL." *Cancers*, 2021, vol. 13, no. 6, article 1280. https://doi.org/10.3390/cancers13061280.

[52] Fusco, Nicola *et al.* "PTEN alterations and their role in cancer management: are we making headway on precision medicine?" *Genes*, June 2020, vol. 11, no. 7, article 719. https://doi.org/10.3390/genes11070719.

[53] Lee, Y. *et al.* "Regulatory mechanisms governing the autophagy-initiating VPS34 complex and its inhibitors." *Biomolecules & Therapeutics*, November 2024, vol. 32, no. 6, pp. 723–735. https://doi.org/10.4062/biomolther.2024.094.

[54] Chen, Dan *et al.* "Death-associated protein kinase 1 as a promising drug target in cancer and Alzheimer's disease." *Recent Patents on Anti-Cancer Drug Discovery*, 2019, vol. 14, no. 2, pp. 144–157. https://doi.org/10.2174/1574892814666181218170257.

[55] Jain, Vaibhav *et al.* "Recent advances in targeting autophagy in cancer." *Trends in Pharmacological Sciences*, 2023, vol. 44, no. 5, pp. 290–302. https://doi.org/10.1016/j.tips.2023.02.003.

[56] Lan, Y. *et al.* "Viral subversion of selective autophagy is critical for biogenesis of virus replication organelles." *Nature Communications*, 2023, vol. 14, no. 1, article 2698. https://doi.org/10.1038/s41467-023-38377-w.

[57] Chen, Xin *et al.* "Development of proteasome inhibitors for cancer therapy." *International Journal of Drug Discovery and Pharmacology*, 2024, vol. 3, no. 1, article 100004. https://doi.org/10.53941/ijddp.2024.100004.

[58] Poillet-Perez, Léa *et al.* "Author correction: Autophagy maintains tumour growth through circulating arginine." *Nature*, 2019, vol. 565, no. 7737, p. E3. https://doi.org/10.1038/s41586-018-0815-6.

[59] Sagnier, S. *et al.* "Autophagy restricts HIV-1 infection by selectively degrading Tat in CD4+ T lymphocytes." *Journal of Virology*, 2015, vol. 89, no. 1, pp. 615–625. https://doi.org/10.1128/JVI.02174-14.

[60] Chakraborty, S. *et al.* "Molecular mechanisms in regulation of autophagy and apoptosis in view of epigenetic regulation of genes and involvement of liquid-liquid phase separation." *Cancer Letters*, 2024, vol. 587, article 216779. https://doi.org/10.1016/j.canlet.2024.216779.

[61] Wang, Songyun and Ding Xue. "Asymmetric partitioning of persistent paternal mitochondria during cell divisions safeguards embryo development and mitochondrial inheritance." *Developmental Cell*. 2025. https://doi.org/10.1016/j.devcel.2025.01.013.

[62] Tettamanti, G. *et al*. "Autophagy in development and regeneration: role in tissue remodelling and cell survival." *The European Zoological Journal*. 2019, vol. 86, no. 1, pp. 113–131. https://doi.org/10. 1080/24750263.2019.1601271.

[63] Gerada C. and K.M. Ryan. "Autophagy, the innate immune response and cancer." *Molecular Oncology*. 2020, vol. 14, no. 9, pp. 1913–1929. https://doi.org/10.1002/1878-0261.12774.

[64] Locatelli, A.G. and S. Cenci. "Autophagy and longevity: evolutionary hints from hyper-longevous mammals." *Frontiers in Endocrinology*. 2022, vol. 13, article 1085522. https://doi.org/10.3389/fendo.2022.1085522.

[65] Palmer, J.E. *et al*. "Autophagy, aging and age-related neurodegeneration." *Neuron*. 2025, vol. 113, no. 1, pp. 29–48. https://doi.org/10.1016/j.neuron.2024.09.015.

[66] Kouroumalis, E. *et al*. "Autophagy in liver diseases." *World Journal of Hepatology*. 2021, vol. 13, no. 1, pp. 6–65. https://doi.org/10.4254/wjh.v13.i1.6.

[67] Bielawska, M. *et al*. "Autophagy in heart failure: insights into mechanisms and therapeutic implications." *Journal of Cardiovascular Development and Disease*. 2023, vol. 10, no. 8, article 352. https://doi.org/10.3390/jcdd10080352.

[68] Yasasilka, X.R. and M.S. Lee. "Role of β-cell autophagy in β-cell physiology and the development of diabetes." *Journal of Diabetes Investigation*. 2024, vol. 15, no. 6, pp. 656–668. https://doi.org/10.1111/jdi.14184.

[69] Ma, C. *et al*. "Crohn's disease-associated ATG16L1 T300A genotype is associated with improved survival in gastric cancer." *EBioMedicine*. 2021, vol. 67, article 103347. https://doi.org/10.1016/j.ebiom.2021.103347.

[70] Nazeer, B. *et al*. "Emerging role of lipophagy in liver disorders." *Molecular and Cellular Biochemistry*. 2024, vol. 479, no. 1, pp. 1–11. https://doi.org/10.1007/s11010-023-04707-1.

[71] Yang, L. *et al*. "Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance." *Cell Metabolism*. 2010, vol. 11, no. 6, pp. 467–478. https://doi.org/10.1016/j.cmet.2010.04.005.

[72] Cai, J. *et al*. "Autophagy ablation in adipocytes induces insulin resistance and reveals roles for lipid peroxide and Nrf2 signaling in adipose-liver crosstalk." *Cell Reports*. 2018, vol. 25, no. 7, pp. 1708–1717.e5. https://doi.org/10.1016/j.celrep.2018.10.040.

[73] Friuli, M. *et al*. "Autophagy and inflammation: an intricate affair in the management of obesity and metabolic disorders: evidence for novel pharmacological strategies?" *Frontiers in Pharmacology*. 2024, vol. 15, article 1407336. https://doi.org/10.3389/fphar.2024.1407336.

[74] Cao, Z. *et al*. "Beclin-1: a therapeutic target at the intersection of autophagy, immunotherapy and cancer treatment." *Frontiers in Immunology*. 2024, vol. 15, article 1506426. https://doi.org/10.3389/fimmu.2024.1506426.

[75] Koizume, S. and Y. Miyagi. "Adaptation mechanisms in cancer: lipid metabolism under hypoxia and nutrient deprivation as a target for novel therapeutic strategies (Review)." *Molecular Medicine Reports*. 2025, vol. 31, no. 4, article 83. https://doi.org/10.3892/mmr.2025.13448.

[76] Sun, K. *et al*. "Paradoxical roles of autophagy in different stages of tumorigenesis: protector for normal or cancer cells." *Cell and Bioscience*. 2013, vol. 3, no. 1, article 35. https://doi.org/10.1186/2045-3701-3-35.

[77] Walweel, N. and O. Aydin. "Enhancing therapeutic efficacy in cancer treatment: integrating nanomedicine with autophagy inhibition strategies." *ACS Omega*. 2024, vol. 9, no. 26, pp. 27832–27852. https://doi.org/10.1021/acsomega.4c02234.

[78] Zeh, H.J. *et al*. "A randomized phase II preoperative study of autophagy inhibition with high-dose hydroxychloroquine and gemcitabine/nab-paclitaxel in pancreatic cancer patients." *Clinical Cancer Research*. 2020, vol. 26, no. 13, pp. 3126–3134. https://doi.org/10.1158/1078-0432.CCR-19-4042.

[79] Yan, X. *et al*. "Autophagy—cell survival and death." *Advances in Experimental Medicine and Biology*. 2019, vol. 1206, pp. 667–696. https://doi.org/10.1007/978-981-15-0602-4_29.

[80] Joly, J.H. *et al*. "The landscape of metabolic pathway dependencies in cancer cell lines." *PLoS Computational Biology*. 2021, vol. 17, no. 4, e1008942. https://doi.org/10.1371/journal.pcbi.1008942.

[81] Roy, A. *et al*. "Role of autophagy in tumor response to radiation: implications for improving radiotherapy." *Frontiers in Oncology*. 2022, vol. 12, article 957373. https://doi.org/10.3389/fonc.2022.957373.

[82] Wu, S.T. *et al*. "CSC-3436 switched tamoxifen-induced autophagy to apoptosis through the inhibition of AMPK/mTOR pathway." *Journal of Biomedical Science*. 2016, vol. 23, no. 1, article 60. https://doi.org/10.1186/s12929-016-0275-y.

[83] Panwar, V. *et al*. "Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease." *Signal Transduction and Targeted Therapy*. 2023, vol. 8, no. 1, article 375. https://doi.org/10.1038/s41392-023-01608-z.

[84] Gómez-Virgilio, L. *et al*. "Autophagy: a key regulator of homeostasis and disease: an overview of molecular mechanisms and modulators." *Cells*. 2022, vol. 11, no. 15, article 2262. https://doi.org/10.3390/cells11152262.

[85] Galluzzi, L. and D.R. Green. "Autophagy-independent functions of the autophagy machinery." *Cell*. 2019, vol. 177, no. 7, pp. 1682–1699. https://doi.org/10.1016/j.cell.2019.05.026.

[86] Chen, S.Y. *et al*. "zVAD-induced autophagic cell death requires c-Src-dependent ERK and JNK activation and reactive oxygen species generation." *Autophagy*. 2011, vol. 7, no. 2, pp. 217–228. https://doi.org/10.4161/auto.7.2.14212.

[87] Lai, M. *et al*. "Sphingolipid/ceramide pathways and autophagy in the onset and progression of melanoma: novel therapeutic targets and opportunities." *International Journal of Molecular Sciences*. 2019, vol. 20, no. 14, article 3436. https://doi.org/10.3390/ijms20143436.

[88] Newton, J. *et al*. "Revisiting the sphingolipid rheostat: evolving concepts in cancer therapy." *Experimental Cell Research*. 2015, vol. 333, no. 2, pp. 195–200. https://doi.org/10.1016/j.yexcr.2015.02.025.

[89] Pattingre, S. *et al*. "Bcl-2 antiapoptotic proteins inhibit Beclin-1-dependent autophagy." *Cell*. 2005, vol. 122, no. 6, pp. 927–939. https://doi.org/10.1016/j.cell.2005.07.002.

[90] Zhang, J. *et al*. "The anti-apoptotic proteins Bcl-2 and Bcl-xL suppress Beclin-1/Atg6-mediated lethal autophagy in polyploid cells." *Experimental Cell Research*. 2020, vol. 394, no. 1, article 112112. https://doi.org/10.1016/j.yexcr.2020.112112.